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DIRECT BROMINATION OR HYDROXYLATION AT C-11 IN VINCADIFFORMINE AND TABERSONINE DERIVATIVES IN SUPERACIDS

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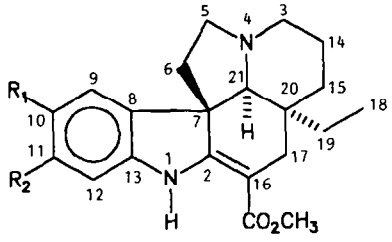
ABSTRACT

In HF-SbF_5, vincadifformine **1b** reacts with H_2O_2 to yield a mixture (60%) of hydroxyderivatives **1c** and **1d**. 2,16-Dihydrovincadifformine **2a** is more selectively hydroxylated at C-11 to give **2b** (40%); in a similar reaction, **2d** yields **2e** (37%). Reaction of **2a** with Br_2 in HF-SbF_5 gives regioselectively compound **2c** (80%).

Synthetic routes to vindoline and beyond to the antitumour agent vinblastine[1,2] remain desirable, especially starting from a readily available substrate such as tabersonine.[3]
We have shown (accompanying paper) that treatment of tabersonine **1a** by H_2O_2 or Br_2 in superacid HF-SbF_5 resulted in an electrophilic attack on the 14, 15 double bond to give fluorohydrins or bromofluoroderivatives.
To circumvent this problem and to bring out the reactivity of the aromatic ring, we used as a model substrate vincadifformine **1b**.
Reaction of **1b** with H_2O_2/HF/SbF_5 resulted, besides the starting material (10%), in a mixture of monohydroxylated products **1c** and **1d** (60%) which could not be separated. Careful examination of the ^1H NMR spectrum of the mixture enabled us to determine the signals of the aromatic protons in **1c** [δ=6.62 (br. s, 11-H and 12-H), δ=6.82 (s, 9-H)] and **1d** [δ=6.35 (dd, J = 8 Hz and 2 Hz, 10-H), δ=6.41 (d, J = 2 Hz, 12-H), δ=7.03 (d, J = 8 Hz, 9-H)]. This poor regioselectivity was not unexpected (compare to hydroxylation of 2,3,3-trimethyl indolenine in similar conditions[5]) and could be highly improved by using 2ß,16ß-dihydrovincadifformine **2a** instead of **1b** as the starting material.[7]

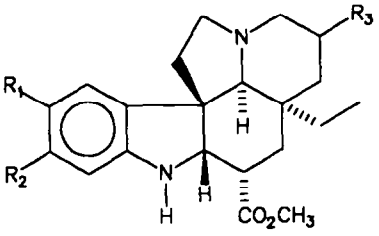


1a 14,15:double bond, $R_1=R_2=H$

1b 14,15:H_2, $R_1=R_2=H$

1c 14,15:H_2, $R_1=OH$, $R_2=H$

1d 14,15:H_2, $R_1=H$, $R_2=OH$



2a $R_1=R_2=R_3=H$

2b $R_1=R_3=H$, $R_2=OH$

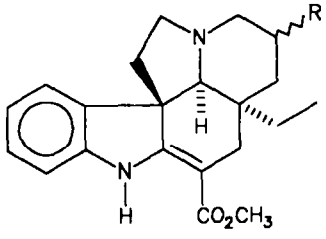
2c $R_1=R_3=H$, $R_2=Br$

2d $R_1=R_2=H$, $R_3=OH$

2e $R_1=H$, $R_2=R_3=OH$

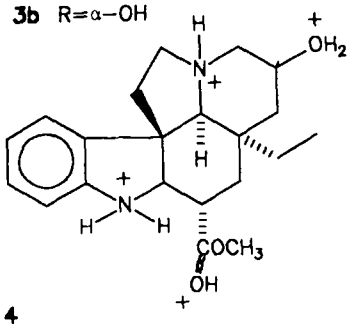
2f $R_1=H$, $R_2=Br$, $R_3=OH$

2g $R_1=R_2=Br$, $R_3=OH$



3a R=β–OH

3b R=α–OH



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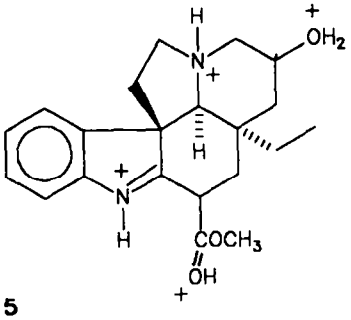

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Hydroxylation by $H_2O_2/HF/SbF_5$ yielded only **2b** (40%) besides the recovered **2a** (37%). Assignment of structure **2b** was made by ^1H NMR, the aromatic hydrogens signals [δ=6.04 (d, J = 2 Hz,12-H),δ=6.14 (dd, J = 8 Hz and 2 Hz, 10-H),δ=6.84 (d, J = 8 Hz, 9-H)], being very similar to those reported in 2,16 dihydro 11-methoxytabersonine[4] and in 6-hydroxy 2,3,3'-trimethylindoline, and very different from those in 5-hydroxy 2,3,3-trimethylindoline.[6]

Indolines have been shown to react with bromine in superacids to give *meta* bromo derivatives, even with a higher regioselectivity at C-6 (indole numbering) (our C-11) than hydroxylation.[6]

A similar reaction on our substrates would be interesting, a bromine atom at C-11 being a good leaving group for nucleophilic substitution (i.e. Br OMe).

Therefore indoline **2a** was treated by $Br_2/HF/SbF_5$ to give regioslectively compound **2c** (80%). As expected ^1H NMR spectrum exhibits signals in the aromatic region [δ=6.62 (s, 12-H),δ=6.76 (d, J = 8 Hz, 10-H),δ=6.86 (d. J = 8 Hz, 9-H)] in agreement with the proposed structure. These signals are very different from those in 10-bromo-2,16 dihydro-TBS[4] and quasi identical to those reported for aromatic hydrogens in 2,3,3-trimethyl 6-bromoindoline.[6]

From a synthetic point of view these regioselective electrophilic aromatic substitutions might be even more interesting if they could be carried out on substrates from which the 14,15 double bond would be more easily generated than from **2b**.

Therefore tabersonine **1a** was hydroxylated by hydroboration-oxidation to give 14ß-hydroxyvincadifformine **3a** (20%) and its epimer **3b** (80%).[7] The major product was chosen for the next step, its dehydration readily regenerating the 14,15 double bond, whereas its isomer **3a** yields a rearranged product.[8]

Subsequent reduction of the 2,16 double bond in alcohol **3b** by using sodium cyanoborohydride/acetic acid yielded 14ß-hydroxy 2,16-dihydrovincadifformine[7] **2d**.

Hydroxylation of indoline **2d** with $H_2O_2/HF/SbF_5$ gave, after usual work-up, the 11-hydroxy analogue **2e** (37%) along, with the starting material (25%).

Here again the ^1H NMR spectrum was particularly revealing and showed an AMX system [δ=6.08 (d,J = 1.7 Hz, 12-H),δ=6.18 (dd, J = 8 Hz and 1.7 Hz, 10-H),δ=6.84 (d, J = 8 Hz, 9-H)], establishing the location of the OH-group.

Bromination of indoline **2d** by $Br_2/HF/SbF_5$ appeared to be more complex. After usual work-up, analytical HPLC showed three products (relative yields 22/56/22) which were isolated over SiO_2 :

- 10,11-dibromo 14ß-hydroxy 2,16-dihydrovincadifformine **2g** (8.5%). In the ^1H NMR spectrum the resonances dues to the aromatic hydrogens [δ=6.77 (s, 9-H),δ=7.18 (s, 12-H)], are in agreement with the postulated structure.

- 11-bromo 14ß-hydroxy 2,16-dihydrovincadifformine **2f** (31%). In the aromatic region, ^1H NMR spectrum exhibits signals [δ=6.64 (d, J = 1.6 Hz, 12-H),δ=6.78 (dd, J = 7.7 Hz and 1.6Hz, 10-H),δ=6.87 (d, J = 7.7 Hz, 9-H)] identical with those in **2c** (*vide supra*).

- starting material **2d** (10%).

Furthermore bromination of 10-bromo 2,16-dihydrotabersonine by Br_2/AcOH yielded 10,12-dibromoderivative whose aromatic hydrogens signals in ^1H NMR [δ=7.02, J = 2 Hz, 9-H),δ=7.28, J = 2 Hz, 11-H)] are those expected by calculation using the starting material reference compound[4], thus confirming substitution in compound **2g**.

With the intention of improving the yield of compound **2f** we attempted selective hydrogenolysis of compound **2g**, the reaction being stated to occur preferentially *ortho* or *para* to the nitrogen group in anilines.[9] Unfortunately, hydrogenolysis conducted with a mixture of compounds **2f** and **2g** in AcOEt by H_2/Pd/C resulted in a mixture of 2a and 2g, compound **2f** reacting faster then **2g**.
In usual conditions, tabersonine and vincadifformine react with electrophiles preferentially at C-10 or C-16[10], and their 2,16 dihydroderivatives at C-10.[4]
In superacidic media such as HF/SbF_5, polyprotonation should occur in all these substrates. Under such acidic conditions, we can expect for example formation of species such as **4** and **5**[5,6,11,12], from **2d** and **3b** respectively, which are the more functionalized starting materials used in this study. Protonations protect the substrate from any degradation,, eventually observed with less functionalized substrates. Whereas alcohols are known to cleave easily over -30°C[13], indoline **2b** is stable (loss of water from its protonated form **4** would have created a highly energetic species by increasing repulsion of positive charges).
Our results make clear that use of superacids can modify dramatically reactivity of alkaloids : direct electrophilic substitution at C-11 can be carried out, making tabersonine a convenient precursor for vindoline and beyond for derived antitumour agents.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Melting points were determined on a Tottoli Büchi 510 melting point apparatus and are uncorrected. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker WP 200 SY spectrometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (Me_4Si) as standard. Low resolution mass spectra were obtained on a Kratos MS 25 spectrometer (relative peak heights are given in brackets for each m/z).
High resolution mass spectra were performed by "Service Central d'Analyse du CNRS de Lyon".
Control of purity were performed on silica gel plates (Kieselgel 60 F_{254}, 0.2 mm).
Separations and purifications were carried out by column chromatography on SiO_2 (Merck Kieselgel 60 0.063-0.2 mm) or by medium pressure chromatography on SiO_2 Kieselgel 60 Type H) with a Jobin-Yvon Chromatospac Prep 10 apparatus.

GENERAL PROCEDURE FOR HYDROXYLATION OF COMPOUNDS 1b,2a and 2d BY H_2O_2 IN SbF_5/HF

To a mixture of SbF_5 (41.5 mmol-9g) and HF (475 mmol-9g) at 0°C was slowly added the substrate (1 mmol), then 80% hydrogen peroxide (2 mmol - 2 eq.). After 15 minutes of reaction, 80% hydrogen peroxide (2 mmol - 2 eq.) were again added. The reaction mixture was

stirred at 0°C for again 15 minutes. After hydrolysis on a mixture $H_2O/NaHCO_3$/ice and extraction with Et_2O or CH_2Cl_2, products were isolated by chromatography over SiO_2.

HYDROXYLATION OF DIHYDRO-2,16 VINCADIFFORMINE 2a

After usual work-up, the reaction mixture was chromatographed over SiO_2. (Eluant : hexane/Et_2O).

- Elution with hexane/Et_2O (70/30; v/v) gave the starting material **2a** (126 mg - 37%).
- Elution with hexane/Et_2O (40/60; v/v) gave the 11-hydroxy 2,16-dihydrovincadifformine **2b** (145 mg - 40%).

m.p : 215-219°C; NMR ($CDCl_3$) : 0.51 (t, J = 7.2 Hz, 18-H), 3.72 (s, CO_2Me), 6.04 (d, J = 2 Hz, 12-H), 6.14 (dd, J = 8 Hz and 2 Hz, 10-H), 6.84 (d, J = 8 Hz, 9-H). MS : m/z = 356(2.4), 270(4.1), 124(100); High Resolution MS : Found 356.2101; Calc. for $C_{21}H_{28}O_3N_2$ 356.20998.

HYDROXYLATION OF 14B-HYDROXY 2,16-DIHYDROVINCADIFFORMINE 2d

After usual work-up the mixture was chromatographed over SiO_2 (eluant $MeOH/CH_2Cl_2$).
- The mixture $MeOH/CH_2Cl_2$ (1/99; v/v) gave the starting material **2d** (90 mg - 25%).
- The mixture $MeOH/CH_2Cl_2$ (2/98; v/v) gave the 11-hydroxy analogue **2e** (138 mg - 37%).

m.p :190-195°C; NMR ($CDCl_3$) : 0.54 (t, J = 7.2 Hz, 18-H), 3.70 (s, CO_2Me), 6.08 (d, J = 1.7 Hz, 12-H), 6.18 (dd, J = 8 Hz and 1.7 Hz, 10-H), 6.84 (d, J = 8 Hz, 9-H). MS : m/z = 372(4.7), 286(8.6), 149(8.7), 141(9.8), 140(100). High Resolution MS : Found 372.2048. Calc. for $C_{21}H_{28}O_4N_2$ 372.2049.

GENERAL PROCEDURE FOR BROMINATION OF COMPOUNDS 2a AND 2d BY Br_2 IN SbF_5/HF

Bromine (0.5 eq. for monobromination or 1 eq. for dibromination) and the substrate **2a** or **2d** (1 mmol) were added slowly to a mixture of SbF_5 (27.7 mmol - 6g) and HF (737 mmol - 14g). The reaction mixture was stirred at 0°C for 60 minutes. After hydrolysis on a mixture $H_2O/NaHCO_3$/ice and extraction with CH_2Cl_2, products were isolated by chromatography over SiO_2.

Bromination of 2,16-dihydrovincadifformine 2a

After usual work-up, the crude product (380 mg) was chromatographed on SiO_2 (eluant Hexane/Et_2O, 60/40; v/v) to yield :
11-bromo 2,16-dihydrovincadifformine **2c** (335 mg - 80%), amorphous glass.
NMR ($CDCl_3$) : 0.52 (t, J = 7.2 Hz, 18-H), 3.71 (s, CO_2Me), 6.62 (s, 12-H), 6.76 (d, J = 8 Hz, 10-H), 6.86 (d, J = 8 Hz, 9-H). MS : m/z = 420(1.8), 418(1.9), 334(5.8), 332(5.9), 125(8.7), 124(100). High Resolution MS : Found 418.1262. Calc. for $C_{21}H_{27}O_2N_2Br$ 418.1256.

Bromination of 14ß-hydroxy 2,16-dihydrovincadifformine 2d

After usual work-up, the separation by medium pressure chromatography (Eluant : MeOH/CH_2Cl_2, 0.5/99.5; v.v) yielded successively :

- 10,11-dibromo 14ß-hydroxy 2,16-dihydrovincadifformine **2g** (45 mg - 8.5%), yellow foam. NMR ($CDCl_3$) : 0.56 (t, J = 7.2 Hz, 18-H), 3.71 (s, CO_2Me), 6.77 (s, 9-H), 7.18 (s, 12-H). MS : m/z = 516(1.3), 514(2.8), 512(1.9), 430(2.7), 428(5.2), 426(3.5), 141 (12.3), 140(100). High Resolution MS : Found 512.03062, Calc. for $C_{21}H_{26}O_3N_2Br$ 512.03099.

-11-bromo 14ß-hydroxy 2,16-dihydrovincadifformine **2f** (31%-135 mg), amorphous glass. NMR ($CDCl_3$) : 0.56 (t, J = 7.2 Hz, 18-H), 3.71 (s, CO_2Me), 6.64 (d, J = 7.7 Hz, 12-H), 6.78 (dd, J = 7.7 Hz and 1.6 Hz, 10-H), 6.87 (d, J = 7.7 Hz, 9-H). MS : m/z = 436 (11.9), 434 (12.4), 405 (4.1), 403(4.0), 350(26.6), 348(27.3), 141(52), 140(100). High Resolution MS : Found 434.12041, Calc. for $C_{21}H_{27}O_3N_2Br$ 434.12049.

- Starting material **2a** (36mg - 10%)

When using one equivalent of Br_2 under similar reaction conditions, only compound **2g** was obtained (80%).

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